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Abstract

Background:

Asthma is common in both children and adults in the Western world, just like anxiety and depression. While some research has revealed that these diseases might share important environmental and pathophysiological aspects, the exact mechanisms still remain unclear.

Objective:

To study the correlation firstly between depression or anxiety and asthma diagnosis in adult twins, and secondly the association between parental depression or anxiety and offspring asthma in children of twins.

Methods:

In total, 24,685 adult twins aged 20-47 years were interviewed or completed a web-based questionnaire and their children were identified through the Multi-Generation Register. Asthma diagnosis was obtained from the Patient Register and the Prescribed Drug Register. Assessment of depression and anxiety was obtained from questionnaires using Center for Epidemiologic Studies Depression Scale (CES-D), Major Depression and Generalized Anxiety Disorder (GAD) from DSM-IV. The association between depression or anxiety and asthma was analyzed with logistic regression adjusting for confounders in twins and offspring. To address genetic and familial environmental confounding we performed a co-twin analysis using disease-discordant twin pairs.

Results:

We found an association between asthma and CES-D, major depression and GAD, e.g. adjusted OR for major depression and register-based asthma 1.56(1.36-1.79). Most of the point estimates remained in the co-twin control analysis, indicating that the association was

likely not due to genetic or familial environmental factors. There was no association between parental depression and/or anxiety and asthma diagnosis in the offspring which implies lack of genetic confounding.

Conclusions:

We found an association between own asthma diagnosis and anxiety or depression, but not with offspring asthma. Our results indicate that the associations were not due to confounding from genes or environment shared by the twins.

Keywords

CESD, Childhood asthma, Generalized anxiety, Major depression, Offspring asthma, Twin study

Abbreviations

BMI	body mass index
CES-D	Center for Epidemiologic Studies Depression Scale
CI	confidence interval
DZ	dizygotic
GAD	Generalized anxiety disorder
HR	hazard ratio
LISA	The Longitudinal integration database for health insurance and labor market studies
MBR	Medical Birth Register

MD	Major Depression
MGR	Multi Generation Register
MZ	monozygotic
OR	odds ratio
PAR	Patient Register
SPDR	Swedish Prescribed Drug Register
STAGE	The Study of Twin Adults: Genes and Environment
STR	Swedish Twin Registry
WHO	World health organization

Introduction

The prevalence of asthma among both adults and children is high in many countries around the world [1, 2]. Depression is also a common disease [3] and several studies have found a correlation between asthma and depression [4-7] [8]. Anxiety disorders with generalized anxiety (GAD) defined as an excessive worry and anxiety [9] is common as well and as reviewed by ten Thoren et al there is a higher incidence of anxiety disorders in asthmatic patients [10]. The association between asthma and depression/anxiety is not clearly understood even though several studies have been performed. As reviewed by Di Marco emerging evidence that the diseases share similar environmental and pathophysiological mechanisms suggest interactions between behavioral, neural, endocrine and immune processes [11].

Previous studies on the association between parental depression or anxiety and asthma in offspring have found higher risk of asthma in children in relation to prenatal maternal stress [12-14], maternal stress reported during the child's first year of life [15, 16] and parental depression [17, 18]. Moreover, children exposed to maternal stress during pregnancy or postpartum had an increased risk for wheezing, but children exposed during both periods showed a threefold increase in odds of infant wheeze, suggesting that a more prolonged period of maternal distress is even more likely to increase the risk of childhood wheeze [19]. We have recently reported from a nationwide population-based study that boys born to mothers with loss of an older child during the second trimester had 50% higher risk of asthma event at both 1-4 years and 7-12 years [20].

Genetic and environmental effects may play an important role in the association between depression or anxiety and offspring asthma, and have not yet been thoroughly

studied. The understanding of the influence of genes and familial environment for an association can be improved by using twin design. In a co-twin control design you use the co-twin of an affected twin as a control. Thereby you can adjust your estimates for confounding factors that the twins share, including factors that are unmeasured or even unmeasurable, e.g. genes and childhood environment. Stratification by zygosity may give further insight with regard to the relative importance of confounding by genes and family environment, since dizygotic twins share 50% of their segregating genes and monozygotic 100%.

We have previously studied adult twins and their spouses and adolescent children, and found some association between self-reported maternal anxiety and subjectively reported offspring asthma or breathlessness which may be due to familial effects [21]. This can be further studied in a population of adult twins and their children where a co-twin control design may help differentiate between environmental and genetic confounding of an association between depression or anxiety and offspring asthma.

To better understand if depression and/or anxiety could be causally associated with asthma in adults, we aimed to study the association between anxiety or depression and asthma diagnosis with adjustment for identified confounders. Further we also aimed to study the association between parental depression and/or anxiety and current or subsequent childhood asthma in the offspring and address genetic and shared environmental confounding using co-twin controls.

Methods

Study design and study population

The Study of Twin Adults: Genes and Environment (STAGE) study population was derived from the Swedish Twin Registry (STR). During 2005-2006 twins born 1959-1985 were invited to participate in an extensive telephone interview or web-based questionnaire on habits, diseases, diet, living conditions, work etc. to assess the impact of gene and environment on future development of different diseases [22]. The National Board of Health and Welfare holds several registers with information about demography and health. In the Swedish Prescribed Drug register (SPDR) all prescribed drugs dispensed at Swedish pharmacies since July 1, 2005 are included. The Patient Register (PAR) covers all public, in-patient care in Sweden from 1987 and onwards. In 2001 an out-patient part was included which covers approximate 75 % of the out-patients visits. The majority of Swedish children with asthma are followed by pediatricians in out-patient clinics. The Medical Birth Register (MBR) covers data on >98 % of all births in Sweden. The Personal Identity Number (PIN), unique for each resident, allows unambiguous linkage between these registers and registers held by Statistic Sweden such as the Multi-Generation Register (MGR) with links between parent and child and the Longitudinal integration database for health insurance and labor market studies (LISA by Swedish acronym) with data on integrating labor market, social sector, as well as educational data for all inhabitants 16 years or older with annual updates.

To derive our study population, firstly twins included in STAGE were defined as our twin cohort. Secondly they were linked to the MGR to identify those that were parents. Thirdly their children were identified from the MBR and defined as our offspring cohort. Additional data on the twins and their children was collected from the MBR and LISA and

subsequent development of childhood asthma obtained from the PAR (asthma diagnosis) and SPDR (asthma medication).

Adopted children were excluded. Twins who moved out of the country after the questionnaire was answered were also excluded. Twins that could not be linked between the registers were also excluded from further analyses.

Variables

Parental depression or anxiety was assessed using self-reported scales for depression and anxiety included in the STAGE questionnaire.

Depression was defined with two different scales, firstly through the Center for Epidemiologic Studies Depression Scale (CES-D), an index of self-reported depressive symptoms in the last week. Originally developed by Radloff in 1977, the 20 item scale was considered to be too long and therefore short versions are more frequently used. We used the eleven-item Iowa short version, validated by Kohout [23]. Each item can give a score of 0-3 points, maximum total 33 points. A score larger than 8 was classified as a possible mild to moderate depression and a score equal or more than 12 was regarded as a possible major depression. We allowed two missing items, and the score of these two items were calculated using imputation of the mean of the individual's response to the non-missing items of the scale. If an individual's response had more than two missing items the score was set to missing. Secondly with the DSM-IV criteria for Major Depression where the specific symptoms of depression (such as depressed mood (feels empty, sad, hopeless, tearful), sleep disturbance (insomnia/hypersomnia), markedly diminished interest or pleasure from almost every activity, significant weight change (up/down) or change of appetite (increased/decreased), feeling inhibited or agitated, feeling of lack of energy, feeling of guilt

or worthlessness, diminished ability to concentrate, recurrent thoughts about death or suicide) were evaluated [24, 25]. To get a positive score at least 5 of the symptoms (at least one of depressed mood or loss of interest or pleasure) must have been present during at least two weeks, during most of the day every day and caused a significant impact of the patient's daily life. The symptoms should not be attributable to grief, abuse of drugs, medication or other somatic disease or injury and caused clinically significant distress or impairment in social, occupational or other important areas of functioning.

General Anxiety Disorder (GAD) according to DSM-IV criteria [24, 25] was categorized as positive when the symptoms of excessive anxiety and worry for specific situations or activities, which were difficult to control, were present during most of the day, almost every day in the last 6 months. In addition to this the patient had three or more of the following symptoms: feeling restless or on edge, easily get fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance (difficulty falling or staying asleep or restless unsatisfying sleep). The anxiety, worry or physical symptoms caused clinically significant distress or impairment in social, occupational or other important areas of functioning and were not attributable to grief, abuse of drugs, medication or other somatic disease or injury.

Outcomes

Register-based asthma in the adult twins was derived from the PAR and defined if ICD code: J45 and J46 as a primary or secondary diagnosis) and/or prescription of asthma drugs in the SPDR, defined as either: 1) any asthma medication except β_2- agonist dispensed at least twice, or 2) any asthma medication dispensed at least three times during one calendar year 2006-2010, identified with the Anatomical Therapeutic Chemical (ATC) codes R03BA (inhaled corticosteroids), R03AK (fixed combinations of β2-agonist and corticosteroids),

R03DC (leukotriene receptor antagonists) or R03AC (β_2- agonist). Dispensed asthma medication from the SPDR and register based asthma diagnoses in PAR are suitable proxies for asthma diagnosis, according to a recently published validation study by Örtqvist et al [26].

Self-reported asthma was obtained from the STAGE questionnaire, defined if the question "do you have asthma?" was yes, and clarified further with current or previous symptoms, thus as in "asthma ever". By the usage of two different variables we created an objective diagnosis that occurred after the STAGE questionnaire was answered as well as a more subjective one that occurred previously. We were also able to define a larger number of asthma cases, including those with a mild asthma.

The ICD codes are applied related to a diagnosis given either at hospital or emergency facilities but also in out-patient specialist clinics.

In the offspring younger than 4.5 years of age, childhood asthma was derived from the PAR and defined if ICD code: J45 and J46 as a primary or secondary diagnosis and prescription of asthma drugs in the SPDR, defined as either: 1) any asthma medication except β_2- agonist dispensed at least twice with at least two weeks between distributions, or 2) any asthma medication dispensed at least three times during one calendar year 2006-2010, identified with the Anatomical Therapeutic Chemical (ATC) codes R03BA, R03AK, R03DC and R03AC. We used this definition to avoid misclassification of asthma in younger children with obstructive bronchiolitis due to respiratory infections.

For children > 4.5 years childhood asthma was defined according to the adult definition above.

Covariates

Covariates were collected from STR (twin age, gender, zygosity), the STAGE questionnaire (smoking and BMI), the MBR (child birth weight, age and gender), and from

LISA (educational level) and categorized as follows: parental age at the time of questionnaire (19-25, 26-30, 31-35, 36-40, 41-45, >46), gender (Male/Female), BMI (<18,5, 18.5-24,9, 25-29,9, >30 kg/m^2 or missing), smoking (yes, no or missing) and educational level; middle school 9 years or shorter, high school 3 years or shorter, college studies shorter than 3 years, college graduates or higher education or missing), and child age at the time of questionnaire (0-4.5, >4.5-12, >12-18, >18).

Statistical analysis

Firstly, logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CIs) for the association between anxiety/depression and own asthma diagnosis. Crude estimates are reported together with estimates adjusted for age, gender, bmi and educational level while using robust standard errors to account for clustering of observations within twin pairs.

Secondly, for the association between parental anxiety or depression and offspring asthma we estimated ORs adjusted for age of child, parental educational level, parental smoking, parental asthma and parental gender while using robust standard errors to account for clustering of observations within families.

We studied possible effect modification by parental gender by testing for interaction with parental depression or anxiety and offspring asthma using likelihood ratio test.

Co-twin controls was used to estimate the association between depression or anxiety and asthma when controlling for genetic (100% for MZ and 50% for DZ) and family environmental effects. We used conditional logistic regression to estimate ORs among twins

discordant for both exposure and outcome and we adjusted for BMI and educational level. Twins with unknown zygosity were excluded from these analyses.

Statistical analyses were conducted using Stata release12.1 (Stata Corp, College Station, TX, USA). .

Permission for the study was obtained from the Regional Ethical Review board in Stockholm, Sweden.

Results

In total, 25,383 twins (59.6%) responded to the questionnaire. Register data was available for 24,685 twins, 44.2 % of them were male and 15,720 had 32,561 biological children, according to the registers.

Table 1 displays background characteristics of the twins. The prevalence of BMI >30 kg/m^2 was 5.1 % and 22.0 % were overweight with BMI 25-29, 9. Those with the lowest level of education had the highest incidence of asthma. The prevalence of mild to moderate CESD was 13.4% and major CESD reported by 16.6%. In total, 3964 twins (16.1%) filled the criteria for Major Depression, for GAD the number was 950 (3.8%). The prevalence of register-based asthma defined from asthma medication in the Prescribed Drug Register and/or diagnose in the Patient Registry was 5.9% in twins. The prevalence of self-reported asthma in the questionnaire was 9.8%.

Table 2 displays general characteristics of the children of the twins. The prevalence of register based childhood asthma was 6.7 %.

Table 3 displays the associations between depression or anxiety and asthma diagnosis in the adult twins. There was a significant association between most measures of depression or anxiety and register-based or self-reported asthma outcomes. For example, there was an association between major CESD and register-based asthma that remained after adjusting for potentially confounding factors, adjusted OR 1.42(95% CI 1.23-1.64) and similarly for self-reported asthma. There was also an increased risk of register-based asthma diagnosis in twins with major depression, adjusted OR 1.56 (95% CI 1.36-1.79) and was stable also for self-reported asthma. In the group of twins with GAD, we found an even higher

risk of register based asthma compared to twins without GAD, adjusted OR 1.73 (95 % CI 1.37-2.19), and this was also similar in the group with self-reported asthma.

Table 4 displays the association between parental depression or anxiety in the twins and asthma in their children. There was no association between any measures of depression or anxiety in the adult twins and register-based asthma in their children. For example, children of parents with mild to moderate CES-D did not have an increased risk of asthma, adjusted OR 1.03 (95% CI 0.90-1.18). The results were similar for parents with major depression as well for those with GAD diagnosis. We also performed a sub analysis in this group with children age 0-6 and age 11-22 years old, with similar estimates. For the studied associations, there was no effect modification by parental sex.

The result of the co-twin control analysis for the association between asthma diagnosis and depression or anxiety in the adult twins is displayed in table 5. In general, point estimates found in cohort analyses remained in the co-twin analyses although with broad confidence intervals and mostly not statistically significant.

For register-based asthma, (n=530 twin pairs) the association between major CESD and asthma after adjustment for confounders was OR 1.20 (0.87-1.65). There was an association between major depression and asthma that remained after adjusting for all confounders, adjusted OR 1.97 (95% CI 1.41-2.76). When stratifying by zygosity there was no significant difference in ORs between MZ and DZ. There was a significant association between parental GAD and register-based asthma, crude OR 1.71 (1.00-2.93) but this result did not remain significant after adjusting for measured confounders.

For self-reported asthma (n=666 twin pairs), there was an association between major CESD and asthma in MZ + DZ twins, which remained significant after adjusting for confounders, adjusted OR 1.44(95% CI 1.10-1.89). When stratifying on zygosity the association only remained in the group with DZ twins, with an adjusted OR 2.01 (95% CI

1.21-3.35). However, the difference between MZ and DZ pairs was not statistically significant. There was an association between major depression and asthma outcomes, crude OR 1.28 (95 % CI 1.00-1.62) but this did not remain significant after adjusting for confounders, and for GAD we found no statistically significant association with self-reported asthma.

Discussion

We found a clear association between depression or anxiety and asthma in twins, and this result remained significant after adjusting for confounding factors. The point estimates remained in the co-twin analyses, which indicates that the association was not due to confounding from genes or shared environmental factors. There was no association between parental depression and/or anxiety and asthma diagnosis in the offspring which along with the co-twin analysis implies lack of genetic confounding.

Our finding that there is an association between depression and asthma and between anxiety and asthma is in line with previous studies [4-7],[10] [27, 28]. As reviewed by Di Marco et al [11] this correlation has been confirmed in a large cross-sectional worldwide study and present research is focusing on the interaction between emotional stress, the immune system and the hypothalamic–pituitary–adrenocortical (HPA) and sympathetic–adrenal–medullary (SAM) axes.

We did not find a correlation between parental depression and/or anxiety and offspring asthma. Since previous studies have shown conflicting results it's possible that it depends on the selection of cohort, age groups [15-19, 29] as well as a difference in how offspring asthma diagnosis was determined. Kozyrzkyj et al followed a birth cohort of children until the age of 7, and found that continued exposure to maternal distress was associated with higher incidence of childhood asthma OR 1.25 (95 % CI 1.01-1.55) [15]. They defined childhood asthma as two physician visits for asthma, one hospitalization, or two prescriptions for any asthma medication (incl. b-2 agonist, inhaled corticosteroids, leukotrienes or chromons) at the year of 7. Maternal distress was defined as physicians' visits, hospitalization or prescribed medication for anxiety or depression. Some cohorts only followed children during infancy (until 2 and 3 years of age) which is when transient wheeze is more common than asthma diagnose [16, 17, 19]. Some studies used questionnaires about

asthma diagnose filled by parents themselves [16, 19] which might lead to a subjective diagnose rather than objective.

We have previously shown an association between maternal anxiety and subjectively reported offspring asthma but not with register-based offspring asthma diagnosis or medication [21], which is in line with our results in this study. Some previous studies are made solely on women or on pregnant women [12-14]. Like our study most studies have used self-reported questionnaires to estimate level of parental stress/distress/anxiety and this could lead to problems with classification of exposure, both in terms of over- and underestimating the presence of anxiety or depression. Different scales were used in different cohort which also makes it hard to compare.

More women than men suffer from major depression, as previous research also have found [3, 30-32]. More women also suffer from general anxiety disorder GAD, which also confirms previous results [30]. One of few studies taking both parents in account was Lange et al who studied if maternal and paternal psychosocial stress respectively was associated with childhood asthma in a cohort of Puerto Rican twins and found some evidence of a correlation with both maternal and paternal stress [17] at age 1. However at age 3 years this correlation disappeared for the fathers but remained for maternal stress. In this study the offspring asthma diagnosis was not register based, only subjectively reported by parents.

Our association between depression or anxiety and asthma in twins remained in the co-twin analyses, which indicates that it most likely is causal or due to non-shared environmental factors such as medication, smoking habits, exposure to high levels of air pollution or other diseases. There was no association between parental depression and/or anxiety and asthma diagnosis in the offspring which along with the co-twin analysis implies absence of genetic confounding.

Strengths and limitations

Strengths

Firstly, we used a large cohort which results in enough power in the main analysis and well validated scales helping minimizing the level of misclassification of exposure.

Secondly, due to the usage of register data from PAR and SPDR, we defined a diagnosis of asthma that was obtained after the questionnaire was filled, and we got an objective asthma diagnosis since dispensed asthma medication from the SPDR and register based asthma diagnoses in PAR have high positive predicted values as proxies for asthma diagnosis [26]. We could however miss some of those who were sick but didn't seek care, those who got a diagnosis but got the wrong one, those who had a mild asthma that did not need referral to specialist care or did not need any medication or those who were prescribed medications but did not collect them at the pharmacy or not often enough. The self-reported asthma from STAGE answers to asthma ever and is likely to include at least some of those not captured in the registers; a phenomenon which could be reflected by the higher prevalence of self-reported asthma from STAGE was compared to register-based asthma.

Thirdly we accounted for several important confounding factors such as parental asthma, age, gender as well as smoking, leading to a good level of internal validity. Register-based information about educational level minimizes recall bias.

Fourthly, we performed a twin study including a co-twin control analysis and also studied offspring data. Studying several generations help to provide pieces to the puzzle on disease development.

Limitations

Not all invited twins responded in this cohort, possibly due to the fact that the STAGE questionnaire was extensive, and also contained many questions of sensitive character, which might lead to less answers that are true or loss of answers. There is also a risk of differential ascertainment such that a twin with depression/anxiety could be more likely to receive asthma diagnosis than a twin without depression. Such misclassification could lead to overestimation of the association between asthma and depression.

Non-responders were more often male, from a lower educational level, had at least one parent born abroad or had been admitted for psychiatric disorders to a higher degree than responders. We lack information on asthma status in the non-responders. However, unless the differences between responders and non-responders are large with regard to both diseases, we would not expect large biases in the associations [33].

In the co-twin analysis, numbers were small which gave us low power, in particular for detecting differences in associations between MZ and DZ twins.

Self-reported data about depression and/ or anxiety might lead to misclassification of exposure, even though the scales in the questionnaire had high validity. Physician diagnosis of depression or GAD would of course be optimal. In PAR data from primary health care facilities are not included, which is where many patients with mild/moderate asthma normally would seek help. They would however be found in the SPDR if they used enough medication so this should not affect the result [26].

Asthma is a chronic disease causing breathlessness and one could argue that depression/anxiety could be a response to that. Depressive symptoms are also described as a possible side effect of inhaled corticosteroid treatment, however we found stable estimates related to all asthma outcomes regardless of medication. Furthermore, we could not establish the temporal sequence of the phenotypes asthma and depression/anxiety. Nor did we have information about atopic asthma. We could not thoroughly account for both parents since we

had information only about one of them and, as always, residual confounding can not be ruled out.

Generalizability

Generalizability regarding twin studies can be argued, but as indicated in recent studies twins [34] [35] [36] higher risk of asthma compared to singletons appears to be due to lower gestational age and birth weight.

Future studies

A new study with information about the mother before and during pregnancy, followed by annual questionnaires for both parents as well as bio samples like saliva-cortisol from both parents and child, use of registers for information about birth data, siblings, socioeconomic status, asthma diagnose as well as depression/ anxiety could lead to new insights.

Conclusions

We found a significant correlation between own asthma and GAD and major depression, and most point estimates remained when using co-twin controls. This indicates that the association could not be explained by familial environment and genes shared by twins. We did not find a correlation between parental depression and/or anxiety and offspring asthma.

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The authors have no conflict of interest to declare.

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Figure 1 Flow chart of the cohort

Figure 1.

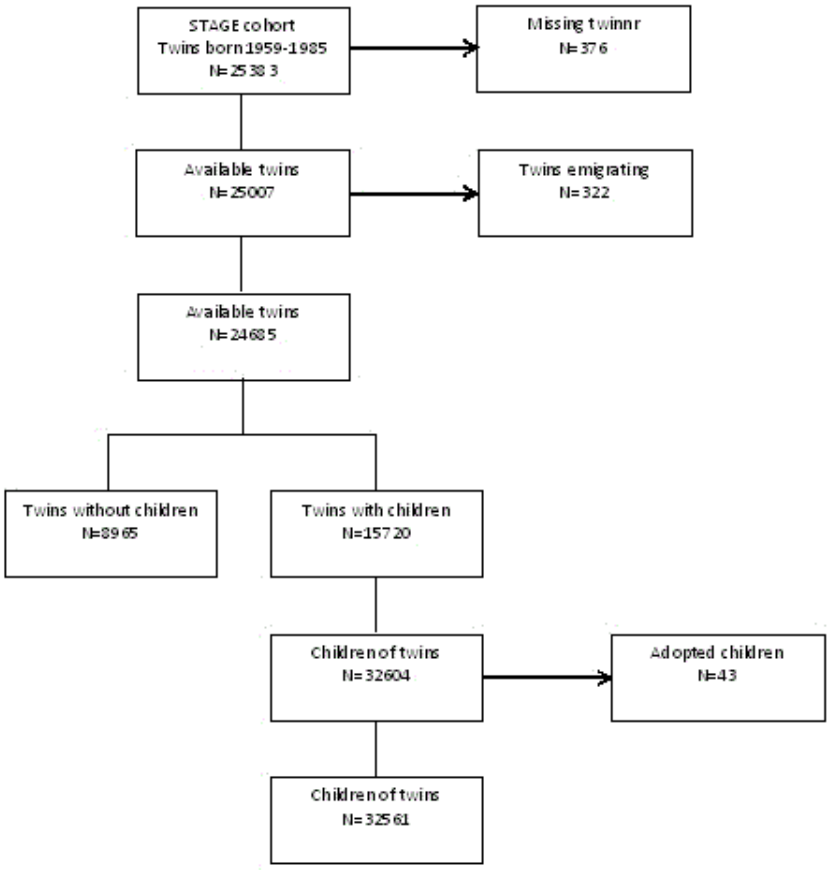

Table 1: General information of STAGE twins

	Total, N (%)	Register-based Asthma, N (%)		Self-reported Asthma, N (%)		
		No	Yes	No	Yes	Missing
Age						
19-25	3171 (12.8)	3019 (13.0)	152 (10.4)	2305 (12.3)	361 (15.0)	505 (15.0)
26-30	4383 (17.8)	4136 (17.8)	247 (16.7)	3194 (17.1)	504 (20.9)	685 (220.4)
31-35	4396 (17.8)	4157 (17.9)	239 (16.3)	3358 (17.9)	413 (17.1)	625 (18.6)
36-40	4672 (18.9)	4370 (18.8)	302 (20.6)	3576 (19.1)	440 (18.3)	656 (19.5)
41-45	5263 (21.3)	4942 (21.3)	321 (21.9)	4097 (21.9)	462 (19.2)	704(21.0)
>46	2800 (11.3)	2596 (11.2)	204 (13.9)	2192 (11.7)	229 (9.5)	379 (11.3)
Gender						
Male	10905 (44,2)	10410 (44.8)	495 (31.0)	8239 (44.0)	974 (40.4)	1692 (47.6)
Female	13780 (55,8)	12810 (33.8)	970 (66.2)	10483 (56.0)	1435 (59.6)	1862 (52.4)
BMI						
<18.5	577 (2.3)	543 (2.3)	34 (2.3)	477 (2.5)	44 (1.8)	56 (1.6)
18.5-24.9	15164 (61.4)	14367 (61.9)	797 54.4)	12229 (65.3)	1464 (60.8)	1471 (41.4)
25-29.9	5433 (22.0)	5097 (21.9)	336 (22.9)	4387 (23.4)	584 (24.2)	462 (13.0)
>30	1272 (5.1)	1111 (4.8)	161 (11.0)	954 (5.1)	199 (8.3)	119 (3.3)
Missing	2239 (9.1)	2102 (9.0)	137 (9.3)	675 (3.6)	118 (4.9)	1446 (40.7)
Smoking						
Non smokers	18435 (74.7)	17409 (75.0)	1026 (70.0)	14254 (76.1)	1780 (73.9)	2401 (67.5)
Regular smokers [1]	5321 (21.6)	4941 (21.3)	380 (25.9)	4028 (21.5)	561 (23.3)	732 (20.6)
Missing	929 (3.8)	870 (3.7)	59 (4.0)	440 (2.3)	68 (2.8)	421 (11.8)
Education Sun 2000 Level						
Middle school	1495 (6.1)	1386 (6.0)	109 (7.4)	1086 (5.8)	168 (7.0)	241 (7.2)
High school	11964 (48.5)	11249 (48.4)	715 (48.8)	9012 (48.1)	1202 (49.9)	1750 (52.2)
College < 3 years	4469 (18.1)	4210 (18.1)	259 (17.7)	3416 (18.2)	435 (18.0)	618 (18.4)
College graduates/higher education > 3 years [2]	6487 (26.3)	6115 (26.3)	372 (25.4)	5015 (26.8)	576 (23.9)	896 (26.7)
Missing	270 (1.1)	260 (1.1)	10 (0.7)	193 (1.0)	28 (1.2)	49 (1.5)
CES-D						
No	14181 (57.4)	13423 (57.8)	758 (51.7)	12312 (65.8)	1406 (58.4)	463 (13.0)
Mild to moderate	3317 (13.4)	3103 (13.3)	214 (14.6)	2852 (15.2)	387 (16.1)	78 (2.2)
Major	4109 (16.6)	3772 (16.2)	337 (23.0)	3387 (18.1)	593 (24.6)	129(3.6)
Missing	3078 (12.5)	2922 (12.6)	156 (10.6)	171 (0.9)	23 (0.9)	2884 (81.1)
Major Depression						
No	17373 (70.4)	16455 (70.9)	918 (62.6)	15108 (80.7)	1789 (74.3)	476 (13.4)
Yes	3964 (16.1)	3597 (15.5)	367 (25.0)	3210 17.1)	577 (23.9)	177 (5.0)
Missing	3348 (13.6)	3168 (13.6)	180 (12.3)	404 (2.1)	43 (1.8)	2901 (81.6)
GAD						
No	20714 (83.9)	19610 (84.4)	1104 (75.3)	15517 (82.9)	1868 (77.5)	3329 (93.7)
Yes	950 (3.8)	849 (3.6)	101 (6.9)	768 (4.1)	148 (6.1)	34 (0.9)
Missing	3021(12.2)	2761 (11.9)	260 (17.7)	2437 (13.0)	393 (16.3)	191(5.4)

[1] Smoke daily and who have smoked at least 28 cigarettes in a month

[2] Including doctoral and licentiate degree

Table 2: General information of children of STAGE twins

	Total, N (%)	**Asthma in children, N (%)**	
		No	Yes
Age			
0-4.5	6100 (9.2)	5822 (19.1)	278 (12.8)
>4.5-12	10875 (14.0)	10073 (33.1)	802 (36.9)
>12-18	8176 (25.1)	7507 (24.7)	669 (30.8)
>18	7410 (22.8)	6987 (23.0)	423 (19.5)
Gender			
Boys	15730 (48.3)	14790 (48.7)	940 (43.3)
Girls	16831 (51.7)	15599 (51.3)	1232 (56.7)
Exposed to parental CES-D			
No	19759 (60.7)	18423 (60.6)	1336 (61.5)
Mild to moderate	4154 (12.7)	3859 (12.7)	295 (13.6)
Major	4758 (14.6)	4444 (14.6)	314 (14.4)
Missing	3890 (11.9)	3663 (12.0)	227 (10.4)
Major Depression			
No	23437 (72.0)	21861 (71.9)	1576 (72.5)
Yes	4887 (15.0)	4528 (14.9)	352 (16.2)
Missing	4244 (13.0)	4000 (13.2)	244 (11.2)
GAD			
No	27615 (84.8)	25775 (84.8)	1840 (84.7)
Yes	1111 (3.4)	1033 (3.4)	78 (3.6)
Missing	3835 (11.8)	3581 (11.8)	254 (11.7)

Table 3: Odds ratios and 95 % confidence intervals for the association between parental anxiety/depression and asthma in STAGE-twins

	Register-based Asthma			Self-reported Asthma		
	Crude OR (95% CI)	Adj * OR (95 % CI)	Adj ^^ OR (95 % CI)	Crude OR (95% CI)	Adj * OR (95 % CI)	Adj ^^ OR (95 % CI)
CES-D						
No	1.00	1.00	1.00	1.00	1.00	1.00
Mild to moderate	1.22 (1.04-1.42)	1.25 (1.07-1.47)	1.24 (1.05-1.46)	1.19 (1.05-1.34)	1.17 (1.04-1.32)	1.17 (1.03-1.33)
Major	1.58 (1.38-1.81)	1.56 (1.36-1.79)	1.42 (1.23-1.64)	1.53 (1.38-1.70)	1.48 (1.33-1.64)	1.42 (1.27-1.58)
Major Depression						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.83 (1.61-2.07)	1.70 (1.49-1.93)	1.56 (1.36-1.79)	1.52 (1.37-1.68)	1.49 (1.35-1.66)	1.44 (1.29-1.61)
GAD						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	2.11 (1.70-2.62)	1.98 (1.60-2.46)	1.73 (1.37-2.19)	1.60 (1.33-1.92)	1.56 (1.29-1.87)	1.44 (1.18-1.75)

* adjusted for age & gender
^^ adjusted for age, gender, bmi, educational level, smoking

Table 4: Odds ratios and 95 % confidence intervals for the association between parental anxiety/depression and asthma in children of STAGE-twins

	Asthma in children		
	Crude OR (95 % CI)	Adj OR † (95 % CI)	Adj OR¤ (95 % CI)
CES-D			
No	1.00	1.00	1.00
Mild to moderate	1.05 (0.92-1.20)	1.05 (0.92-1.20)	1.03 (0.90-1.18)
Major	0.97 (0.86-1.11)	0.97 (0.86-1.11)	0.93 (0.81-1.06)
Major Depression			
No	1.00	1.00	1.00
Yes	1.08 (0.96-1.21)	1.09 (0.96-1.23)	1.06 (0.94-1.20)
GAD			
No	1.00	1.00	1.00
Yes	1.06 (0.84-1.34)	1.07 (0.84-1.35)	0.99 (0.78-1.27)

† adjusted for child age
¤ adjusted for parental (smoking, gender, educational level, parents own asthma) + child age

Table 5: Co-twin analysis of asthma in STAGE-twins exposed to anxiety and depression

Outcome	**Register-based asthma** (n=530 twin pairs)				**Self-reported asthma** (n= 666 twin pairs)			
MZ+DZ	Exposure asthma twin	Crude OR (95% CI)	Exposure asthma twin	Adj OR * (95 % CI)	Exposure asthma twin	Crude OR (95% CI)	Exposure asthma twin	Adj OR * (95 % CI)
CES-D	221		190		290		252	
No	83	1.00	74	1.00	105	1.00	91	1.00
Mild /moderate	60	1.17 (0.85-1.62)	52	1.13 (0.80-1.60)	81	1.09 (0.84-1.42)	70	1.11 (0.84-1.48)
Major	78	1.32 (0.63-1.58)	64	1.20 (0.87-1.65)	104	1.43 (1.12-1.82)	91	1.44 (1.10-1.89)
Major Depression	129		111		187		164	
No	44	1.00	38	1.00	85	1.00	77	1.00
Yes	85	2.10 (1.54-2.85)	73	1.97 (1.41-2.76)	102	1.28(1.00-1.62)	87	1.20 (0.92-1.56)
GAD	36		26		44		36	
No	14	1.00	9	1.00	19	1.00	15	1.00
Yes	22	1.71 (1.00-2.93)	17	1.67 (0.88-3.22)	25	1.53 (0.95-2.47)	21	1.46 (0.85-2.48)
MZ	Exposure asthma twin	Crude OR (95% CI)	Exposure asthma twin	Adj OR* (95 % CI)	Exposure asthma twin	Crude OR (95% CI)	Exposure asthma twin	Adj OR* (95 % CI)
CES-D	117		100		146		129	
No	44	1.00	38	1.00	54	1.00	48	1.00
Mild /moderate	30	1.14 (0.66-1.96)	26	1.05 (0.58-1.88)	44	1.27 (0.81-2.01)	38	1.21 (0.75-1.96)
Major	43	1.17 (0.74-1.86)	36	1.14 (0.67-1.94)	48	1.28 (0.83-1.98)	43	1.46 (0.90-2.38)
Major Depression	65		54		91		43	
No	23	1.00	19	1.00	45	1.00	21	1.00
Yes	42	1.83 (1.10-3.04)	35	1.83 (1.02-3.29)	46	1.02 (0.68-1.54)	22	1.01 (0.64-1.60)
DZ	Exposure asthma twin	Crude OR (95% CI)	Exposure asthma twin	Adj OR * (95 % CI)	Exposure asthma twin	Crude OR (95% CI)	Exposure asthma twin	Adj OR * (95 % CI)
CES-D	104		90		144		123	
No	39	1.00	36	1.00	51	1.00	43	1.00
Mild /moderate	30	1.15 (0.67-1.97)	26	1.19 (0.64-2.20)	37	1.06 (0.67-1.68)	32	1.14 (0.68-1.91)
Major	35	1.25 (0.75-2.10)	28	1.10 (0.61-1.97)	56	1.89 (1.20-2.99)	48	2.01 (1.21-3.35)
Major Depression	64		57		96		87	
No	21	1.00	19	1.00	40	1.00	38	1.00
Yes	43	2.05 (1.21-3.45)	38	1.91 (1.09-3.37)	56	1.40 (0.93-2.10)	49	1.23 (0.80-1.90)

* adjusted for bmi, educational level, smoking